STABLE GABAPENTIN COMPOSITIONS

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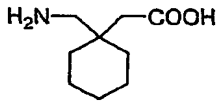
Field of Invention

This invention is concerned with stable gabapentin compositions. More particularly, this invention is concerned with pharmaceutical compositions comprising a therapeutically effective amount of gabapentin and an excipient which is not detrimental to the long-term stability of gabapentin.

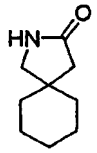
BACKGROUND OF THE INVENTION

Gabapentin (I) and its pharmaceutically acceptable salts have been used for a number of years for the treatment of cerebral disorders such as epilepsy, fainting attacks, hypokinesis and cranial traumas, has been known for many years, for example as disclosed in US-A-4024175, US-A-4087544 and US-A-4894476.



(I)

US-A-6054482 discloses that the preparation and long-term storage of gabapentin and its pharmaceutically acceptable salts present problems since (i) during the preparation the compounds show considerable variations without apparent reason; (ii) very pure gabapentin, when stored long term, shows differing stabilities; and (iii) a toxic lactam (II) is formed when the gabapentin degrades. Pharmaceutically acceptable gabapentin compositions must comprise no more than 0.5% by weight of this toxic lactam compound.



(II)

To combat lactam formation and provide long-term stability in pharmaceutical compositions, US-A-6054482 teaches that the following procedures must be maintained:

1. The active gabapentin materials must be prepared as highly purified, non-derivatized free amino acids, for example from the corresponding hydrochloride by ion exchange. The proportion of remaining hydrochloride admixtures, or anions of other mineral acids, should thereby not exceed 20 ppm;
2. To suppress the formation of toxic lactam, a particular excipient must be used.

Under the above storage conditions generally applicable for medicaments, toxic lactam formation does not increase within a period of time of 1 year after production of the pharmaceutical composition or of the active material by more than 0.2 % by wt and preferably 0.1 % by wt, based on the weight of the pure active material.

In addition, US-A-6054482 provides a specific list of excipient materials which do not influence the stability of the active gabapentin compound when the proportion of mineral acid does not exceed 20 ppm. These are: hydroxypropylmethyl cellulose, polyvinyl pyrrolidone, crospovidone, poloxamer 407, poloxamer 188, sodium starch glycolate, copolyvidone, maize starch, cyclodextrin, lactose, talc as well as co-polymers of dimethylamino-methacrylic acid and neutral methacrylic acid ester. It also provides a specific list of excipient materials which reduce the stability of the active gabapentin compounds: these are modified maize starch, sodium croscarmellose, glycerol behenic acid ester, methacrylic acid co-polymers (types A and C), anion exchangers, titanium dioxide, and silica gels such as Aerosil 200.

US-A-6531509 discloses that the long-term stability of pharmaceutical compositions based on active gabapentin compounds is not affected by the nature of the excipient materials disclosed in US-A-6054482 provided that the amount of mineral acid anion in the composition is in excess of 20 ppm.

It is desired that pharmaceutical compositions are very stable, so that they can be offered for sale with very long shelf lives. It is also preferred that stable, pharmaceutically active compositions are not limited to pre-determined amounts of mineral acid anion. Neither US-A-6054482 nor US-A-6531509 suggest that the compositions disclosed therein may be stable for very long periods e.g. for at least two years, irrespective of the amount of mineral acid anion or excipient.

We now report pharmaceutically effective gabapentin compositions which are stable for very long periods of time i.e. compositions to contain less than 0.5% lactam after at least two years of storage at 25°C and 60% atmospheric humidity. Stability results for different durations and temperatures are included hereinafter.

SUMMARY OF THE INVENTION

Accordingly, the present invention provides a stable pharmaceutical composition of gabapentin, stable in storage for extended periods, under conditions selected from the ranges consisting of: storage for at least 3 years at 25°C and 60% relative humidity, storage for at least 2 years at 30°C and 60% relative humidity, and storage for at least 6 months at 40°C and 75% relative humidity.

According to another aspect of the present invention there is provided a pharmaceutical composition comprising gabapentin and microcrystalline cellulose as the sole excipient. Alternatively, the composition also comprises a lubricant, such as magnesium stearate.

According to another aspect of the present invention there is provided a pharmaceutical composition comprising gabapentin and microcrystalline cellulose as the sole diluent.

Preferably the composition is in the form of a capsule.

Preferably the capsule comprises hard gelatin.

Preferably the composition of the hard gelatin capsule further comprises one or more of: methyl hydroxy benzoate; propyl hydroxyl benzoate, titanium oxide, yellow iron oxide, red iron oxide, in any suitable combinations. The composition of the gelatin capsule may also contain purified water.

According to another aspect of the present invention there is provided a pharmaceutical composition comprising gabapentin and excipients including microcrystalline cellulose and magnesium stearate. Preferably, these are the only excipients, in which case microcrystalline cellulose is regarded as a diluent and magnesium stearate as a lubricant.

According to another aspect of the present invention there is provided a pharmaceutical composition comprising gabapentin and one or more of the following as a diluent: dibasic calcium phosphate; tribasic calcium phosphate; calcium sulphate; mannitol; microcrystalline cellulose; starch; and lactose.

According to another aspect of the present invention there is provided a pharmaceutical composition comprising gabapentin and one or more of the following as a lubricant: magnesium stearate; stearic acid; and colloidal silicon dioxide.

According to another aspect of the present invention there is provided a pharmaceutical composition comprising gabapentin and sodium lauryl sulphate.

According to another aspect of the present invention there is provided a pharmaceutical composition comprising gabapentin, the composition further comprising:

(i) microcrystalline cellulose;
(ii) magnesium stearate; and
(iii) sodium lauryl sulphate.

In certain embodiments, this composition also contains colloidal silicon dioxide.

The content of mineral acid anions may be less than 70 ppm, and more preferably less than 50 ppm or 30 ppm. These ranges are not intended to be limiting and contents outside these ranges can be used.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Table Titles

The invention shall now be described further by way of exemplification.

Experimental Protocols

HPLC Assay for Related Substances

Chromatographic Conditions

Column

YMC–ODS – AQ, 5μm, 250 mm X 4.6 or equivalent

Column Temperature

Ambient

Mobile Phase

0.025 M Potassium Phosphate Monobasic (pH 6.0): Methanol (70:30)

Detector

UV at 210 nm

Flow rate

10ml/minute

Injection volume

50 μl

Run Time

10 minutes or as appropriate for Standard Solution

15 minutes or as appropriate for Resolution Solution

70 minutes or as appropriate for Lactam Marker, Test Solution and Diluent Solutions.

Needle wash Solution

Water:methanol (70:30)

Mobile Phase Preparation

0.025M potassium phosphate, monobasic (KH_2PO_4) buffer solution pH 6.0:

Weight about 6.8g of potassium phosphate, monobasic (KH_2PO_4) and dissolve in about 1800 ml of water. Adjust pH of the solution to 6.0 (±0.05) using 1 N Sodium Hydroxide solution. Add sufficient water to make 2000 ml and mix well.

Mobile Phase: Mix 1400 ml of 0.025 M potassium phosphate, monobasic (KH_2PO_4) buffer solution pH 6.0 with 600 ml methanol, filter and degas.

Sample Solution Preparation

Weigh 20 intact capsules. Empty the capsules as completely as possible into a suitable container. Clean and weigh the empty capsule shells and determine the average capsule filled weight. Mix thoroughly the combined contents of the capsules.

Weigh accurately amount of powder equivalent to 600 mg Gabapentin into a 50 ml volumetric flask. Add about 30 ml of mobile phase and sonicate for 10 minutes with intermittent shaking to disperse the powder. Shake for 30 minutes. Dilute to volume with mobile phase and mix well. Filter the solution.

Standard Solution Preparation

- Stock Standard Solution

  Weigh accurately about 25 mg Gabapentin R.S. and transfer to 50 ml volumetric flask. Add to it about 25 ml mobile phase. Sonicate to dissolve, make up the volume with mobile phase.

- Working Standard Solution

  Pipette out 6ml of the solution from Standard Stock Solution into 50 ml volumetric Flask. Dilute to volume with mobile phase and mix well.

Resolution Solution Preparation

- Resolution stock solution (C.A.M)

Weigh accurately about 12.5 mg of C.A.M., dissolved and dilute to 25 ml with methanol

Note : Store under refrigeration for future use. The solution may be used as long as a peak due to C.A.M. is clearly visible in the chromatogram.

- Resolution working solution

Pipette out 6 ml of Standard Stock Solution and 6 ml of C.A.M. Stock Solution and dilute to 50 ml with mobile phase.

Lactam Marker Solution Preparation

- Lactam stock solution

Weigh accurately about 12.5 mg lactam, dissolve and dilute to 25 ml with methanol.

Note : Store under refrigeration for future use. The solution may be used as long as the lactam peak is clearly seen.

- Lactam working solution

Pipette 6 ml of Lactam Stock solution and dilute to 50 ml with mobile phase.

Preparation of Methyl Parabens Marker Solution

Weigh accurately about 25 mg of methyl parabens and dissolve and dilute to 50 ml with mobile phase. Pipette 5 ml of solution into a 50 ml volumetric flask and make up to volume with mobile phase. Further pipette 5 ml and dilute to 50 ml with mobile phase.

System Suitability

System suitability test solution: Inject 50 µl of Resolution Solution into the equilibrated chromatograph. Calculate the system suitability requirements. Gabapentin peak has retention time of about 6 minutes. C.A.M. has retention time of about 10 minutes

The resolution between Gabapentin and C. A. M. peaks is NLT 4.5

- The tailing factor (T), determined from the Gabapentin peak is NMT 2.0%. Perform 6 replicate injections of 50 µl of Working Standard Solution. The System precision is acceptable if the RSD of 6 replicate standard injections is NMT 5.0%

Procedure

Separately inject 50 µl of the mobile phase, Standard Solution, lactam marker solution, Methyl Parabens marker solution and Test Solutions into the Chromatograph. Measure the responses of the major peaks.

Calculate the content of impurity lactam: single largest individual/unidentified impurity/degradant and total impurities/degradant.

Note: Identify the peak due to methyl parabens based upon the retention time in the chromatogram of the Methyl Parabens marker solution. Disregard any peak occurring in the test solution at the same RRT as the Methyl Parabens peak.

Calculations

A. Impurity 1: lactam {cyclohexanespiro (4,5) decane - 2, 3 –butyrolactam}

Note:

- Identify the lactam peak based on the retention time in the chromatograms of the Lactam Maker Solution injection.

- Resolve Response Factor for lactam (RRF) = 21

$$\% \text{ Lactam} = \frac{A_T}{A_S} \times \frac{1}{21} \times \frac{Ws}{50} \times \frac{6}{50} \times \frac{P}{100} \times \frac{50}{WT} \times \frac{\text{Average Filled Wt.}}{\text{Label Claim}} \times 100$$

Where,

AT = Peak area of lactam in Test Solution

AS = Peak area of Gabapentin in Standard Solution

P = Potency of Gabapentin W.S.

WS = Weight of Gabapentin W.S. in mg

WT = Weight of Test sample in mg.

B. Single Largest Individual Unidentified Impurities/Degradant

Determine the peak areas for individual impurities/degradant. For the largest peak areas observed other than those of diluent, lactam and Gabapentin peaks

% Single largest individual impurities/degradants

$$\frac{AT}{AS} \times \frac{Ws}{50} \times \frac{6}{50} \times \frac{P}{100} \times \frac{50}{WT} \times \frac{\text{Average Filled Wt.}}{\text{Label Claim}} \times 100$$

Where,

AT = Peak area of any impurity in Test Solution

AS = Peak area of Gabapentin in Standard Solution

P = Potency of Gabapentin W.S.

WS = Weight of Gabapentin W.S. in mg.

WT = Weight of Test sample in mg.

C. Total other impurities/degradants:

Sum the peak areas of all unidentified impurities.

% Total other impurities/degradants =

$$\frac{\Sigma AT}{AS} \times \frac{Ws}{50} \times \frac{6}{50} \times \frac{P}{100} \times \frac{50}{WT} \times \frac{\text{Average Filled Wt.}}{\text{Label Claim}} \times 100$$

Where,

ΣAT = Peak area of any impurity in Test Solution

AS = Peak area of Gabapentin in Standard Solution

P = Potency of Gabapentin W.S.

WS = Weight of Gabapentin W.S. in mg.

WT = Weight of Test sample in mg.

D. % Total impurities/degradant :

= % lactam + % total other impurities/degradants

Medicinal Products

Exemplary medicinal products containing gabapentin are disclosed in Table 1. Table 1 relates to gabapentin formulations containing active doses at 100, 200 and 400 mg. In hard gelatine capsules. Excipients include microcrystalline cellulose as the sole diluent and magnesium stearate as a lubricant. Table 1 additionally sets out capsule shell constituents and also constituents of the printing ink.

Stability data for the formulations of Table 1 at a range of temperatures (20 °C to 40°C) and durations is provided in Tables 4 through 18.

Composition

Composition of Proprietary Medicinal Product

Table 1: Composition of the proprietary medical product

Name of Ingredients	mg/unit			Function	Reference to standards
	100 mg	300 mg	400 mg		
Active Ingredient					
Gabapentin	100.00	300.00	400.00	Active	HSE
Other Ingredients					
Cellulose, microcrystalline (Avicel PH 200)	11.75	35.25	47.00	Diluent	Ph. Eur.
Magnesium stearate	1.50	4.50	6.00	Lubricant	Ph. Eur.
Total fill weight	**113.25**	**339.75**	**453.00**		
Empty Hard Gelatin Capsule Shell	Size '3'	Size '1'	Size '0'	Capsule shell	HSE
Methyl parahydroxybenzoate (E218)	0.400	0.620	0.784		Ph. Eur.
Propyl parahydroxybenzoate (E216)	0.100	0.155	0.196		Ph. Eur.
Sodium laurilsulfate	0.040	0.062	0.078		Ph. Eur.
Titanium oxide (E171)	1.083	0.839	1.304		Ph. Eur.
Yellow iron oxide (E172)	-	0.465	0.784		HSE
Red iron oxide (E172)	-	-	0.078		HSE
Purified water	7.250	11.238	14.210		Ph. Eur.
Gelatin	41.127	64.121	80.554		Ph. Eur.
Constituents of the printing ink					
Ethanol anhydrous					Ph. Eur.
Isopropyl alcohol					Ph. Eur.
Shellac					Ph. Eur.
Activated charcoal					Ph. Eur.

Stability

Stability Tests on the Finished Product

Quality Specification for the proposed shelf-life

The Stability specification for Gabapentin Capsules 100 mg, 300 mg and 400 mg is presented in Table 2

Table 2: Stability Specification and routine tests for Gabapentin Capsules

Test	Specification		
	100 mg capsule	300 mg capsule	400 mg capsule
Appearance (Visual) *	White/white Size '3' hard gelatin capsules containing white to off white powder printed 'GAB 100' and twin triangle logo in black ink	Yellow/yellow Size '1' hard gelatin capsules containing white to off white powder printed with 'GAB 300' and twin triangle logo in black ink	Orange/orange Size '0' hard gelatin capsules containing white to off white powder printed with 'GAB 400' and twin triangle logo in black ink
Average capsule weight	163.2 mg ± 5%	415.7 mg ± 5%	548.0 mg ± 5%
Average filled weight	113.2 mg ± 5%	339.7 mg ± 5%	453.0 mg ± 5%
Uniformity of filled weight	± 10% of average filled weight	± 7.5% of average filled weight	± 7.5% of average filled weight
Disintegration (Ph. Eur.)	NMT 15 minutes	NMT 15 minutes	NMT 15 minutes
Water content (by KF)	NMT 3%	NMT 3%	NMT 3%
Related Substances (TA 02)			
Lactam	NMT 0.3%	NMT 0.3%	NMT 0.3%
Any other impurities	NMT 0.1%	NMT 0.1%	NMT 0.1%
Total Impurities (including Lactam)	NMT 1.0%	NMT 1.0%	NMT 1.0%
Dissolution (TA 03)	NLT 80% in 20 minutes	NLT 80% in 20 minutes	NLT 80% in 20 minutes
Assay: Content of Gabapentin (TA 05)	95.0-105.0%	95.0-105.0%	95.0-105.0%
Microbial Limits [1]	NMT 1000 bacteria per gm NMT 100 fungi per gm. E.coli – absent	NMT 1000 bacteria per gm NMT 100 fungi per gm. E.coli - absent	NMT 1000 bacteria per gm NMT 100 fungi per gm. E.coli – absent

[1]To be tested on initial, 6, 24 and 36 months.

Batches Tested and Packaging

Table 3: Details of batches put on stability

Capsule strength (mg)	Batch number	Drug substance batch number	Batch size (Capsules)	Date of manufacture	Date on stability test
100 mg	GBC-I/100	28800398 288010498	100,000	April 1999	July 1999
100 mg	GBC-II/100	288010498 288070399	100,000	April 1999	July 1999
300 mg	GBC-I/300	28800398 288010498	100,000	March 1999	May 1999
300 mg	GBC-II/300	288010498 288070399	100,000	April 1999	May 1999
400 mg	GBC-I/400	28800398 288010498	110,000	March 1999	May 1999
400 mg	GBC-II/400	288010498 288070399	110,000	April 1999	May 1999

Active drug substance used for the manufacture of the above batches was supplied from Teva. All batches were manufactured at Nicholas Piramal (Pithampur) Limited, India.

The above stability batches were packed into white opaque PVC/PVdC/Aluminium blister strips. These blister strips were cartooned prior to being placed on test.

Storage Conditions

Real Time Studies

Stability samples were stored at 25°C±2°C/60%±5%RH and 30°C±2°C/60%±5%RH and were tested at initial, 3, 6, 12, 18 and 24 and 36 month time points and 3, 6, 12, 18 and 24 month time points respectively.

Studies under other conditions (Accelerated Conditions)

Stability samples were stored at 40 °C±2°C /75%±5% RH and were tested at initial, 1 month, 2 months, 3 months and 6 months time points.

Evaluation Test Procedures

The analytical methods for all the tests used in the stability studies are the same as proposed for routine batch analysis and are known to persons skilled in the art. The methodology for, related substances and assay has been validated and are suitable for stability purposes.

The assay and related substances methods used throughout the stability studies are stability indicating.

Results of Tests

Results of Physical Testing

The stability data is for 6 months for all strengths at accelerated conditions and for 36 months at 25°C±2°C/60%±5%RH and 24 months at 30°C±2°C/60%±5%RH. The results

of physical testing of the stability batches packed in PVC/PVdC/Aluminium blister packs is shown in Tables 4 to 19.

Throughout the period of study under all the conditions 25 °C±2°C /60%±5%RH, 30°C±2°C /60%±5%RH and 40 °C±2 °C/75%±5%RH, no significant changes were noted in the appearance or disintegration time of any of the samples on test. It is noted none of the stability batches have the markings proposed for marketing, however this does not affect the stability profile.

The percentage water content by KF had shown an increase after one month study in the test samples for 300 and 400 mg strengths.

However, at the end of the second month, once again a similar trend was observed and investigation was initiated as per the SOP for out of specification. The result of the investigation indicated that the test was performed after 6-7 hours of removal of the powder blend from the capsule. The exposure to atmosphere could have resulted in higher values. The statement to the effect that KF should be done on fresh samples only has been included in the method of analysis.

Results of Chemical Testing

Related substances/impurities

The amount of all the secondary peaks obtained was calculated with respect to Gabapentin diluted standard. In the determination of the amount of known impurity i.e. lactam, the higher response of this impurity (RRF=21 relative to gabapentin) was accounted for in the calculation. From Tables 4 to 19, it may be noted that the value for lactam is well below 0.2% up to 3 months interval for all the strengths. However, at the sixth month interval, the values obtained were slightly above 0.2%.

One unknown impurity at a RRT of about 6.0 was noted under accelerated conditions (40°C±2°C/75%±5%RH) at the end of one month. Investigation was taken up with respect to the identification and characterisation of this impurity and it was found to be

due to the preservative, methyl parabens, present in the capsule shells. The methodology was therefore revised to include preparation of a methyl parabens marker solution and to disregard any peaks occurring in the test samples at the same retention time as the marker.

Total impurities were found to be within the shelf life limits proposed.

Dissolution

No significant changes were observed in the dissolution results of any of the samples under test.

Assay

Up to 36 months data at 25°C2±°C /60%±5%RH, 24 months data at 30°C±2°C/60%±5%RH and 6 months at 40°C±2°C/75%±5%RH are available for all strengths of capsules. The data are within specification limits for all the batches.

Table 4: Stability of Gabapentin Capsules 100 mg stored in PVC/PVdC/Aluminium packs (Batch Number GBC-I/100) stored at 25°C±2°C/ 60%±5%RH

Test Performed	Limits	Initial	1 Month	2 Month	3 Month	6 Month	9 Month	12 Month	18 Month	24 Month
Appearance	White/white, Size '3' hard gelatin capsules containing white to off white powder, printed with logo in black ink.	White/white, Size '3' hard gelatin capsules containing white to off white powder, printed with logo in black ink.	NT	NT	As initial	As initial	As initial	As initial	As initial	As initial
Disintegration time	NMT 15 minutes	8-9	NT	NT	8-9	8-9	6-7	7-8	6-7	6-7
Water content (%)	NMT 3%	1.65	NT	NT	1.75	1.82	1.75	1.70	1.51	1.56
Related Substances										
Lactam	NMT 0.3%	NIL	NT	NT	0.040	0.069	0.136	0.146	0.208	0.157
Any other individual impurities	NMT 0.1%	< 0.001	NT	NT	0.002	0.003	0.004	0.004	0.007	0.007
Total Impurities	NMT 1.0%	<0.001	NT	NT	0.085	0.120	0.256	0.277	0.410	0.269
Dissolution	NLT 80% dissolved in 20 minutes	99.80	NT	NT	100.3	99.37	98.54	97.95	100.00	98.99
Assay	95-105%	98.20	NT	NT	98.53	98.78	98.79	98.36	98.56	98.62
Microbial Limits	NMT 1000 bacteria per gm NMT 100 fungi per gm. E.coli - absent	10 CFU / gm. E.coli – absent	NT	NT	NT	NT	NT	NT	NT	NT

NT : Not Tested

Table 5: Stability of Gabapentin Capsules 100 mg stored in PVC/PVdC/Aluminium packs (Batch Number GBC-I/100) stored at 30°C±2°C/ 60%±5%RH

Test Performed	Limits	Initial	1 Month	2 Month	3 Month	6 Month	9 Month	12 Month	18 Month	24 Month
Appearance	White/white, Size '3' hard gelatin capsules containing white to off white powder, printed with logo in black ink.	White/white, Size '3' hard gelatin capsules containing white to off white powder, printed with logo in black ink.	NT	NT	As initial	As initial	As initial	As initial	As initial	As initial
Disintegration time	NMT 15 minutes	8-9	NT	NT	6-7	7-8	7-8	8-9	8-9	8-9
Water content (%)	NMT 3%	1.65	NT	NT	1.70	1.80	1.78	1.69	1.69	1.49
Related Substances										
Lactam	NMT 0.3%	NIL	NT	NT	0.062	0.096	0.136	0.223	0.260	0.267
Any other individual impurities	NMT 0.1%	< 0.001	NT	NT	0.002	0.003	0.004	0.005	0.008	0.009
Total Impurities	NMT 1.0%	<0.001	NT	NT	0.099	0.250	0.252	0.415	0.465	0.363
Dissolution	NLT 80% dissolved in 20 minutes	99.80	NT	NT	87.22	99.29	98.92	99.70	99.80	99.02
Assay	95-105%	98.20	NT	NT	98.32	98.41	98.93	98.92	98.38	98.45
Microbial Limits	NMT 1000 bacteria per gm NMT 100 fungi per gm. E.coli – absent	10 CFU / gm. E.coli – absent	NT	NT	NT	NT	NT	NT	NT	NT

NT : Not Tested

Table 6: Stability of Gabapentin Capsules 100 mg stored in PVC/PVdC/Aluminium packs (Batch Number GBC-I/100) stored at 40°C±2°C/ 75%±5%RH

Test Performed	Limits	Initial	1 Month	2 Month	3 Month	6 Month
Appearance	White/white, Size '3' hard gelatin capsules containing white to off white powder, printed with logo in black ink.	White/white, Size '3' hard gelatin capsules containing white to off white powder, printed with logo in black ink.	As initial	As initial	As initial	As initial
Disintegration time	NMT 15 minutes	8-9	8-9	8-9	8-9	7-8
Water content (%)	NMT 3%	1.65	1.65	1.82	1.84	1.82
Related Substances						
Lactam	NMT 0.3%	NIL	0.064	0.145	0.144	0.206
Any other individual impurities	NMT 0.1%	< 0.001	0.017	0.046	0.061	0.079
Total Impurities	NMT 1.0%	<0.001	0.160	0.334	0.375	0.585
Dissolution	NLT 80% dissolved in 20 minutes	99.80	98.96	97.66	102.6	99.53
Assay	95-105%	98.20	98.46	98.32	98.82	98.94
Microbial Limits	NMT 1000 bacteria per gm NMT 100 fungi per gm. E.coli – absent	10 CFU / gm. E.coli – absent	NT	NT	NT	NT

NT : Not Tested

Table 7: Stability of Gabapentin Capsules 100 mg stored in PVC/PVdC/Aluminium packs

(Batch Number GBC-II/100) stored at 25°C±2°C/ 60%±5%RH

Test Performed	Limits	Initial	1 Month	2 Month	3 Month	6 Month	9 Month	12 Month	18 Month	24 Month
Appearance	White/white, Size '3' hard gelatin capsules containing white to off white powder, printed with logo in black ink.	White/white, Size '3' hard gelatin capsules containing white to off white powder, printed with logo in black ink.	NT	NT	As initial	As initial	As initial	As initial	As initial	As initial
Disintegration time	NMT 15 minutes	6-7	NT	NT	6-7	8-9	6-7	8-9	7-8	8-9
Water content (%)	NMT 3%	1.68	NT	NT	1.85	1.71	1.70	1.65	1.53	1.58
Related Substances										
Lactam	NMT 0.3%	NIL	NT	NT	0.021	0.046	0.097	0.138	0.168	0.155
Any other individual impurities	NMT 0.1%	< 0.001	NT	NT	0.002	0.003	0.004	0.004	0.008	0.007
Total Impurities	NMT 1.0%	<0.021	NT	NT	0.045	0.113	0.214	0.302	0.277	0.278
Dissolution	NLT 80% dissolved in 20 minutes	102.70	NT	NT	106.45	98.85	99.86	100.37	100.03	98.94
Assay	95-105%	98.10	NT	NT	99.58	98.91	98.68	98.65	98.67	98.52
Microbial Limits	NMT 1000 bacteria per gm NMT 100 fungi per gm. E.coli – absent	10 CFU / gm. E.coli – absent	NT	NT	NT	NT	NT	NT	NT	NT

NT: Not Tested

Table 8: Stability of Gabapentin Capsules 100 mg stored in PVC/PVdC/Aluminium packs (Batch Number GBC-II/100) stored at 30°C±2°C/60%±5%RH

Test Performed	Limits	Initial	1 Month	2 Month	3 Month	6 Month	9 Month	12 Month	18 Month	24 Month
Appearance	White/white, Size '3' hard gelatin capsules containing white to off white powder, printed with logo in black ink.	White/white, Size '3' hard gelatin capsules containing white to off white powder, printed with logo in black ink.	NT	NT	As initial	As initial	As initial	As initial	As initial	As initial
Disintegration time	NMT 15 minutes	6-7	NT	NT	7-8	6-7	6-7	8-9	8-9	8-9
Water content (%)	NMT 3%	1.68	NT	NT	1.81	1.78	1.74	1.70	1.57	1.67
Related Substances										
Lactam	NMT 0.3%	NIL	NT	NT	0.030	0.073	0.098	0.208	0.218	0.268
Any other individual Impurities	NMT 0.1%	< 0.001	NT	NT	0.001	0.003	0.004	0.005	0.007	0.010
Total Impurities	NMT 1.0%	<0.021	NT	NT	0.037	0.094	0.213	0.381	0.367	0.344
Dissolution	NLT 80% dissolved in 20 minutes	102.70	NT	NT	109.37	99.01	101.90	99.59	99.79	99.22
Assay	95-105%	98.10	NT	NT	98.93	98.28	98.57	98.53	98.94	98.87
Microbial Limits	NMT 1000 bacteria per gm NMT 100 fungi per gm. E.coli – absent	10 CFU / gm. E.coli – absent	NT	NT	NT	NT	NT	NT	NT	NT

NT: Not Tested

Table 9: Stability of Gabapentin Capsules 100 mg stored in PVC/PVdC/Aluminium packs (Batch Number GBC-II/100) stored at 40°C±2°C/75%±5%RH

Test Performed	Limits	Initial	1 Month	2 Month	3 Month	6 Month
Appearance	White/white, Size '3' hard gelatin capsules containing white to off white powder, printed with logo in black ink.	White/white, Size '3' hard gelatin capsules containing white to off white powder, printed with logo in black ink.	As initial	As initial	As initial	As initial
Disintegration time	NMT 15 minutes	6-7	7-8	6-7	7-8	7-8
Water content (%)	NMT 3%	1.68	1.66	1.87	1.80	1.82
Related Substances						
Lactam	NMT 0.3%	NIL	0.039	0.117	0.103	0.184
Any other individual impurities	NMT 0.1%	< 0.001	0.017	0.043	0.054	0.073
Total Impurities	NMT 1.0%	<0.021	0.221	0.239	0.384	0.579
Dissolution	NLT 80% dissolved in 20 minutes	102.70	103.84	103.8	108.80	98.80
Assay	95-105%	98.10	100.02	99.22	98.84	98.73
Microbial Limits	NMT 1000 bacteria per gm NMT 100 fungi per gm. E.coli – absent	10 CFU / gm. E.coli – absent	NT	NT	NT	NT

NT: Not Tested

Table 10: Stability of Gabapentin Capsules 300 mg stored in PVC/PVdC/Aluminium packs (Batch Number GBC-I/300) stored at 25°C±2°C/ 60%±5%RH

Test Performed	Limits	Initial	1 Month	2 Month	3 Month	6 Month	9 Month	12 Month	18 Month	24 Month
Appearance	Yellow/yellow, Size '1' hard gelatin capsules containing white to off white powder, printed with logo in black ink.	Yellow/yellow, Size '1' hard gelatin capsules containing white to off white powder, printed with logo in black ink.	NT	NT	As initial	As initial	As initial	As initial	As initial	As initial
Disintegration time	NMT 15 minutes	9-10	NT	NT	9-10	8-9	7-8	7-8	6-7	7-8
Water content (%)	NMT 3%	1.19	NT	NT	1.22	1.17	1.12	1.12	1.04	0.90
Related Substances										
Lactam	NMT 0.3%	NIL	NT	NT	0.016	0.032	0.050	0.061	0.099	0.134
Any other individual impurities	NMT 0.1%	< 0.001	NT	NT	<0.001	<0.001	0.001	0.001	0.001	0.002
Total Impurities	NMT 1.0%	0.011	NT	NT	<0.019	<0.088	0.109	0.154	0.293	0.279
Dissolution	NLT 80% dissolved in 20 minutes	102.80	NT	NT	104.62	99.63	99.01	96.14	99.59	98.72
Assay	95-105%	100.40	NT	NT	100.54	98.56	98.60	99.10	99.01	101.06
Microbial Limits	NMT 1000 bacteria per gm NMT 100 fungi per gm. E.coli – absent	10 CFU / gm. E.coli – absent	NT	NT	NT	NT	NT	NT	NT	NT

NT: Not Tested

Table 11: Stability of Gabapentin Capsules 300 mg stored in PVC/PVdC/Aluminium packs (Batch Number GBC-I/300) stored at 30°C±2°C/60%±5%RH

Test Performed	Limits	Initial	1 Month	2 Month	3 Month	6 Month	9 Month	12 Month	18 Month	24 Month
Appearance	Yellow/yellow, Size '1' hard gelatin capsules containing white to off white powder, printed with logo in black ink.	Yellow/yellow, Size '1' hard gelatin capsules containing white to off white powder, printed with logo in black ink.	NT	NT	As initial	As initial	As initial	As initial	As initial	As initial
Disintegration time	NMT 15 minutes	9-10	NT	NT	8-9	9-10	8-9	8-9	8-9	6-7
Water content (%)	NMT 3%	1.19	NT	NT	1.20	1.13	1.14	1.12	1.02	0.89
Related Substances										
Lactam	NMT 0.3%	NIL	NT	NT	0.017	0.043	0.067	0.122	0.176	0.209
Any other individual impurities	NMT 0.1%	< 0.001	NT	NT	<0.001	<0.001	0.001	0.006	0.002	0.003
Total Impurities	NMT 1.0%	0.011	NT	NT	<0.079	<0.093	0.394	0.328	0.465	0.471
Dissolution	NLT 80% dissolved in 20 minutes	102.80	NT	NT	101.6	99.27	101.70	98.14	98.37	99.59
Assay	95-105%	100.40	NT	NT	100.26	99.01	99.01	99.10	98.92	100.54
Microbial Limits	NMT 1000 bacteria per gm NMT 100 fungi per gm. E.coli – absent	10 CFU / gm. E.coli – absent	NT	NT	NT	NT	NT	NT	NT	NT

NT: Not Tested

Table 12: Stability of Gabapentin Capsules 300 mg stored in PVC/PVdC/Aluminium packs (Batch Number GBC-II/300) stored at 30°C±2°C/60%±5%RH

Test Performed	Limits	Initial	1 Month	2 Month	3 Month	6 Month	9 Month	12 Month	18 Month	24 Month
Appearance	Yellow/yellow, Size '1' hard gelatin capsules containing white to off white powder, printed with logo in black ink.	Yellow/yellow, Size '1' hard gelatin capsules containing white to off white powder, printed with logo in black ink.	NT	NT	As initial	As initial	As initial	As initial	As initial	As initial
Disintegration time	NMT 15 minutes	6-7	NT	NT	8-9	7-8	8-9	7-8	7-8	7-8
Water content (%)	NMT 3%	0.54	NT	NT	1.21	1.16	1.12	1.15	1.00	0.96
Related Substances										
Lactam	NMT 0.3%	NIL	NT	NT	0.016	0.037	0.055	0.106	0.144	0.189
Any other individual impurities	NMT 0.1%	<0.001	NT	NT	<0.001	0.002	0.002	0.003	0.002	0.003
Total Impurities	NMT 1.0%	<0.012	NT	NT	<0.177	0.234	0.219	0.209	0.317	0.459
Dissolution	NLT 80% dissolved in 20 minutes	98.06	NT	NT	100.86	95.70	101.38	102.60	102.14	101.92
Assay	95-105%	99.60	NT	NT	98.05	98.04	98.90	99.04	98.71	98.37
Microbial Limits	NMT 1000 bacteria per gm NMT 100 fungi per gm. E.coli – absent	10 CFU / gm. E.coli – absent	NT	NT	NT	NT	NT	NT	NT	NT

NT: Not Tested

Table 13: Stability of Gabapentin Capsules 300 mg stored in PVC/PVdC/Aluminium packs (Batch Number GBC-II/300) stored at 25°C±2°C/ 60%±5%RH

Test Performed	Limits	Initial	1 Month	2 Month	3 Month	6 Month	9 Month	12 Month	18 Month	24 Month
Appearance	Yellow/yellow, Size '1' hard gelatin capsules containing white to off white powder, printed with logo in black ink.	Yellow/yellow, Size '1' hard gelatin capsules containing white to off white powder, printed with logo in black ink.	NT	NT	As initial	As initial	As initial	As initial	As initial	As initial
Disintegration time	NMT 15 minutes	6-7	NT	NT	7-8	7-8	7-8	6-7	7-8	6-7
Water content (%)	NMT 3%	0.54	NT	NT	1.27	1.20	1.14	1.13	1.00	0.92
Related Substances										
Lactam	NMT 0.3%	NIL	NT	NT	0.011	0.028	0.042	0.060	0.066	0.111
Any other individual impurities	NMT 0.1%	<0.001	NT	NT	<0.001	0.001	0.002	0.002	0.002	0.002
Total Impurities	NMT 1.0%	<0.012	NT	NT	<0.126	0.158	0.108	0.233	0.260	0.263
Dissolution	NLT 80% dissolved in 20 minutes	98.06	NT	NT	101.49	97.74	101.66	101.32	99.88	100.60
Assay	95-105%	99.60	NT	NT	98.66	97.87	97.68	98.20	98.65	99.75
Microbial Limits	NMT 1000 bacteria per gm NMT 100 fungi per gm. E.coli – absent	10 CFU / gm. E.coli – absent	NT	NT	NT	NT	NT	NT	NT	NT

NT: Not Tested

Table 14: Stability of Gabapentin Capsules 400 mg stored in PVC/PVdC/Aluminium packs (Batch Number GBC-I/400) stored at 25°C±2°C/60%±5%RH

Test Performed	Limits	Initial	1 Month	2 Month	3 Month	6 Month	9 Month	12 Month	18 Month	24 Month
Appearance	Orange/orange, Size '0' hard gelatin capsules containing white to off white powder, printed with logo in black ink.	Orange/orange, Size '0' hard gelatin capsules containing white to off white powder, printed with logo in black ink.	NT	NT	As initial	As initial	As initial	As initial	As initial	As initial
Disintegration time	NMT 15 minutes	6-7	NT	NT	7-8	6-7	7-8	7-8	7-8	6-7
Water content (%)	NMT 3%	1.19	NT	NT	1.20	1.14	1.20	1.06	1.06	0.99
Related Substances										
Lactam	NMT 0.3%	NIL	NT	NT	0.013	0.025	0.042	0.058	0.074	0.104
Any other individual impurities	NMT 0.1%	<0.001	NT	NT	<0.001	<0.001	0.001	0.001	0.001	0.002
Total impurities	NMT 1.0%	<0.001	NT	NT	<0.099	<0.050	0.187	0.221	0.212	0.196
Dissolution	NLT 80% dissolved in 20 minutes	101.70	NT	NT	99.25	99.20	100.37	98.45	99.64	98.92
Assay	95-105%	101.70	NT	NT	98.30	98.09	98.12	98.52	98.13	99.40
Microbial Limits	NMT 1000 bacteria per gm NMT 100 fungi per gm. E.coli – absent	10 CFU / gm. E.coli – absent	NT	NT	NT	NT	NT	NT	NT	NT

NT: Not Tested

Table 15: Stability of Gabapentin Capsules 400 mg stored in PVC/PVdC/Aluminium packs (Batch Number GBC-I/400) stored at 30°C±2°C/ 60%±5%RH

Test Performed	Limits	Initial	1 Month	2 Month	3 Month	6 Month	9 Month	12 Month	18 Month	24 Month
Appearance	Orange/orange, Size '0' hard gelatin capsules containing white to off white powder, printed with logo in black ink.	Orange/orange, Size '0' hard gelatin capsules containing white to off white powder, printed with logo in black ink.	NT	NT	As initial	As initial	As initial	As initial	As initial	As initial
Disintegration time	NMT 15 minutes	6-7	NT	NT	6-7	7-8	6-7	6-7	7-8	6-7
Water content (%)	NMT 3%	1.19	NT	NT	1.23	1.18	1.08	1.19	1.02	1.00
Related Substances										
Lactam	NMT 0.3%	NIL	NT	NT	0.016	0.037	0.05	0.090	0.125	0.184
Any other individual Impurities	NMT 0.1%	<0.001	NT	NT	0.001	<0.001	0.001	0.002	0.002	0.003
Total Impurities	NMT 1.0%	<0.001	NT	NT	0.234	<0.174	0.171	0.243	0.343	0.410
Dissolution	NLT 80% dissolved in 20 minutes	101.70	NT	NT	100.25	99.20	99.42	97.33	101.28	98.21
Assay	95-105%	101.70	NT	NT	99.35	98.09	98.48	98.14	98.25	97.42
Microbial Limits	NMT 1000 bacteria per gm NMT 100 fungi per gm. E.coli – absent	10 CFU / gm. E.coli – absent	NT	NT	NT	NT	NT	NT	NT	NT

NT: Not Tested

Table 16: Stability of Gabapentin Capsules 400 mg stored in PVC/PVdC/Aluminium packs (Batch Number GBC-I/400) stored at 40°C±2°C/75%±5%RH

Test Performed	Limits	Initial	1 Month	2 Month	3 Month	6 Month
Appearance	Orange/orange, Size '0' hard gelatin capsules containing white to off white powder, printed with logo in black ink.	Orange/orange, Size '0' hard gelatin capsules containing white to off white powder, printed with logo in black ink.	As initial	As initial	As initial	As initial
Disintegration time	NMT 15 minutes	6-7	7-8	7-8	7-8	7-8
Water content (%)	NMT 3%	1.19	1.50	1.52	1.58	1.51
Related Substances						
Lactam	NMT 0.3%	NIL	0.040	0.075	0.080	0.185
Any other individual impurities	NMT 0.1%	<0.001	0.005	0.018	0.014	0.039
Total Impurities	NMT 1.0%	<0.001	0.045	0.460	0.314	0.469
Dissolution	NLT 80% dissolved in 20 minutes	101.70	99.64	101.54	98.93	91.59
Assay	95-105%	101.70	99.28	98.52	97.84	98.23
Microbial Limits	NMT 1000 bacteria per gm NMT 100 fungi per gm. E.coli – absent	10 CFU / gm. E.coli – absent	NT	NT	NT	10 CFU absent

NT: Not Tested

Table 17: Stability of Gabapentin Capsules 400 mg stored in PVC/PVdC/Aluminium packs (Batch Number GBC-II/400) stored at 25°C±2°C/ 60%±5%RH

Test Performed	Limits	Initial	1 Month	2 Month	3 Month	6 Month	9 Month	12 Month	18 Month	24 Month
Appearance	Orange/orange, Size '0' hard gelatin capsules containing white to off white powder, printed with logo in black ink.	Orange/orange, Size '0' hard gelatin capsules containing white to off white powder, printed with logo in black ink.	NT	NT	As initial	As initial	As initial	As initial	As initial	As initial
Disintegration time	NMT 15 minutes	10-11	NT	NT	10-11	10-11	10-11	10-11	9-10	9-10
Water content (%)	NMT 3%	0.54	NT	NT	1.14	1.10	1.05	1.05	1.00	0.95
Related Substances										
Lactam	NMT 0.3%	NIL	NT	NT	0.010	0.028	0.036	0.047	0.066	0.109
Any other individual impurities	NMT 0.1%	NIL	NT	NT	<0.001	0.002	0.002	0.012	0.001	0.002
Total Impurities	NMT 1.0%	NIL	NT	NT	<0.035	0.030	0.059	0.219	0.186	0.195
Dissolution	NLT 80% dissolved in 20 minutes	95.30	NT	NT	98.23	94.06	100.72	99.47	95.80	99.24
Assay	95-105%	101.50	NT	NT	101.70	98.98	98.80	98.54	98.31	99.66
Microbial Limits	NMT 1000 bacteria per gm NMT 100 fungi per gm. E.coli – absent	10 CFU / gm. E.coli – absent	NT	NT	NT	NT	NT	NT	NT	NT

NT: Not Tested

Table 18: Stability of Gabapentin Capsules 400 mg stored in PVC/PVdC/Aluminium packs (Batch Number GBC-II/400) stored at 30°C±2°C/60%±5%RH

Test Performed	Limits	Initial	1 Month	2 Month	3 Month	6 Month	9 Month	12 Month	18 Month	24 Month
Appearance	Orange/orange, Size '0' hard gelatin capsules containing white to off white powder, printed with logo in black ink.	Orange/orange, Size '0' hard gelatin capsules containing white to off white powder, printed with logo in black ink.	NT	NT	As initial	As initial	As initial	As initial	As initial	As initial
Disintegration time	NMT 15 minutes	10-11	NT	NT	11-12	11-12	10-11	10-11	10-11	9-10
Water content (%)	NMT 3%	0.54	NT	NT	1.12	1.10	1.02	1.06	1.00	0.97
Related Substances										
Lactam	NMT 0.3%	NIL	NT	NT	0.013	0.036	0.052	0.072	0.131	0.185
Any other individual Impurities	NMT 0.1%	NIL	NT	NT	<0.001	0.004	0.002	0.019	0.002	0.003
Total Impurities	NMT 1.0%	NIL	NT	NT	<0.174	0.232	0.119	0.516	0.353	0.452
Dissolution	NLT 80% dissolved in 20 minutes	95.30	NT	NT	94.68	94.65	104.31	97.51	98.74	100.15
Assay	95-105%	101.50	NT	NT	101.10	99.21	99.00	98.69	98.29	98.94
Microbial Limits	NMT 1000 bacteria per gm NMT 100 fungi per gm. E.coli – absent	10 CFU / gm. E.coli – absent	NT	NT	NT	NT	NT	NT	NT	NT

NT: Not Tested

Table 19: Stability of Gabapentin Capsules 400 mg stored in PVC/PVdC/Aluminium packs (Batch Number GBC-II/400) stored at 40°C±2°C/ 75%±5%RH

Test Performed	Limits	Initial	1 Month	2 Month	3 Month	6 Month
Appearance	Orange/orange, Size '0' hard gelatin capsules containing white to off white powder, printed with logo in black ink.	Orange/orange, Size '0' hard gelatin capsules containing white to off white powder, printed with logo in black ink.	As initial	As initial	As initial	As initial
Disintegration time	NMT 15 minutes	10-11	11-12	11-12	10-11	11-12
Water content (%)	NMT 3%	0.54	1.54	1.56	1.53	1.52
Related Substances						
Lactam	NMT 0.3%	NIL	0.044	0.083	0.104	0.219
Any other individual impurities	NMT 0.1%	NIL	0.007	0.024	0.023	0.042
Total Impurities	NMT 1.0%	NIL	0.051	0.291	0.627	0.506
Dissolution	NLT 80% dissolved in 20 minutes	95.30	100.48	91.85	99.79	94.10
Assay	95-105%	101.50	101.09	100.38	99.80	99.12
Microbial Limits	NMT 1000 bacteria per gm NMT 100 fungi per gm. E.coli - absent	10 CFU / gm. E.coli – absent	NT	NT	NT	10 CFU absent

NT: Not Tested

Table 20: Stability of Neurontin® Capsules 400 mg stored in PVC/PVdC/Aluminium packs stored at 25°C±2°C /60%±5%RH

Test Performed	Limits	Initial	1 Month	2 Month	3 Month	6 Month	12 Month	18 Month	24 Month
Appearance	Orange/orange, Size '0' hard gelatin capsules containing white to off white powder, printed with Neurontin® 400 mg logo in black ink.	Orange/orange, Size '0' hard gelatin capsules containing white to off white powder, printed with Neurontin® 400 mg logo in black ink.	NT	NT	NT	As initial	As initial	NT	As initial
Disintegration time	NMT 15 minutes	10-11	NT	NT	NT	10-11	9-10	NT	
Water content (%)	NMT 3%	NT	NT	NT	NT	1.38	1.36	NT	
Related Substances									
Lactam	NMT 0.3%	NIL	NT	NT	NT	0.037	0.078	NT	0.113
Any other individual Impurities	NMT 0.1%	<0.001	NT	NT	NT	NIL	0.001	NT	0.109
Total Impurities	NMT 1.0%	<0.001	NT	NT	NT	0.051	0.269	NT	0.378
Dissolution	NLT 80% dissolved in 20 minutes	102.80	NT	NT	NT	93.84	96.60	NT	101.29
Assay	95-105%	98.80	NT	NT	NT	97.10	98.62	NT	98.19
Microbial Limits	NMT 1000 bacteria per gm	NT	NT	NT	NT	NT	NT	NT	NT

NT: Not Tested

Table 21: Stability of Neurontin® Capsules 400 mg stored in PVC/PVdC/Aluminium packs stored at 30°C±2°C/60%±5%RH

Test Performed	Limits	Initial	1 Month	2 Month	3 Month	6 Month	9 Month	12 Month	18 Month	24 Month
Appearance	Orange/orange, Size '0' hard gelatin capsules containing white to off white powder, printed with Neurontin® 400 mg logo in black ink.	Orange/orange, Size '0' hard gelatin capsules containing white to off white powder, printed with Neurontin® 400 mg logo in black ink.	NT	NT	As initial	As initial	As initial	As initial	As initial	As initial
Disintegration time	NMT 15 minutes	10-11	NT	NT	10-11	10-11	9-10	9-10		
Water content (%)	NMT 3%	NT	NT	NT	1.62	1.38	1.40	1.65		
Related Substances										
Lactam	NMT 0.3%	NIL	NT	NT	0.016	0.049	0.071	0.118	0.152	0.190
Any other individual impurities	NMT 0.1%	<0.001	NT	NT	<0.001	<0.001	<0.001	<0.001	<0.001	0.278
Total Impurities	NMT 1.0%	<0.001	NT	NT	<0.072	<0.111	0.134	0.329	<0.374	0.824
Dissolution	NLT 80% dissolved in 20 minutes	102.80	NT	NT	97.80	93.84	99.13	97.78	99.23	101.76
Assay	95-105%	98.80	NT	NT	99.82	97.10	100.01	98.79	98.36	100.10
Microbial Limits	NMT 1000 bacteria per gm	NT	NT	NT	NT	NT	NT	NT		

NT: Not Tested

Table 22: Stability of Neurontin® Capsules 400 mg stored in PVC/PVdC/Aluminium packs stored at 40°C±2°C /75%±5%RH

Test Performed	Limits	Initial	1 Month	2 Month	3 Month	6 Month
Appearance	Orange/orange, Size '0' hard gelatin capsules containing white to off white powder, printed with Neurontin® 400 mg logo in black ink.	Orange/orange, Size '0' hard gelatin capsules containing white to off white powder, printed with Neurontin® 400 mg logo in black ink.	As initial	As initial	As initial	As initial
Disintegration time	NMT 15 minutes	10-11	10-11	10-11	10-11	10-11
Water content (%)	NMT 3%	NT	1.64	1.76	1.44	1.40
Related Substances						
Lactam	NMT 0.3%	NIL	<0.077	0.103	0.135	0.283
Any other individual impurities	NMT 0.1%	<0.001	<0.001	<0.001	0.001	0.004
Total Impurities	NMT 1.0%	<0.001	<0.120	<0.225	0.225	1.084
Dissolution	NLT 80% dissolved in 20 minutes	102.80	99.96	102.20	96.41	93.81
Assay	95-105%	98.80	99.13	100.97	98.64	98.15
Microbial Limits	NMT 1000 bacteria per gm	NT	NT	NT	NT	NT

NT: Not Tested

Stability conclusions

Gabapentin capsules packed into PVC/PVdC/Aluminium blister pack have been shown to be physically and chemically stable for 36 months when stored at 25°C/50%±5%RH, 24 months when stored at 30°C±2°C/60%±5%RH and for 6 months when stored at 40°C±2°C /75%±5%RH.

Proposed Shelf-life

The stability data generated supports the following:

Proposed product shelf-life: 36 months when packed in blister packs.

Labelled storage conditions: none.

Further Exemplary Medicinal Products

Further exemplary medicinal products containing the gabapentin active are disclosed in Tables 23 and 24.

Exemplary trial blends for 400 mg formulations are disclosed e.g. in Table 24.

Tables 25 through 39 show stability data for these further exemplary formulations.

Formulation Development

A capsule formulation was needed which would be linear for all three strengths.

The excipients used in the preformulation studies and the coding are shown in Table 23.

Table 23. Excipients used in the pre-formulation studies

Excipients	Sample code	Binary mixture code
DILUENTS		
1. Dibasic Calcium Phosphate IP (NGRANULES)	D1	GD1
2. Tribasic Calcium Phosphate IP	D2	GD2
3. Calcium Sulphate anhydrous Ph. Eur	D3	GD3
4. Mannitol Ph. Eur	D4	GD4
5. Microcrystalline Cellulose (AVICEL PH 200) Ph. Eur	D5	GD5
6. Starch IP	D6	GD6
7. Lactose (PHARMATOSE) Ph. Eur	D7	GD7
LUBRICANTS		
1. Magnesium Stearate Ph. Eur	L1	GL1
2. Stearic Acid IP	L2	GL2
3. Colloidal Silicon Dioxide Ph. Eur	L3	GL3
SOLUBILIZER		
1. Sodium Lauryl Sulphate IP	S1	GS1
DRUG		
Gabapentin (Recon) HSE	G	
Neurontin® Capsule 400 mg B No. 0015077	NRT	

Two trial blends (Blend I and Blend II) having the composition as shown in Table 24 were also evaluated as per the protocol for pre-formulation trials.

Table 24. Trial blends for pre-formulation studies.

Ingredients	Blend I		Blend II	
	per capsule (mg)	per 50 capsules (g)	per capsule (mg)	per 50 capsules (g)
Gabapentin	400.00	20.00	400.00	20.00
Microcrystalline Cellulose (Avicel PH 200)	133.00	6.65	133.00	6.65
Magnesium Stearate	5.00	0.25	5.00	0.25
Colloidal Silicon Dioxide	2.00	0.10	-	-
Sodium Lauryl Sulphate	0.20	0.01	0.20	0.01

All the ingredients were passed through 20 mesh screen and blended together. The results of all the pre-formulation compatibility studies are given in Tables 25 to 39, including comparative results for the drug substance (Table 39) and UK reference product (Table 38) as controls.

Excipient Compatibility Study Protocol Gabapentin Capsules

Aim: To carry out preformulation excipient compatibility studies for Gabapentin capsules

Controls

Gabapentin drug substance

Samples retained at 4 °C

Individual Excipients

Excipients

Diluents

Dibasic calcium phosphate

Tribasic calcium phosphate

Calcium sulphate

Mannitol

Microcrystalline cellulose

Starch IP

Lactose

Lubricants

Magnesium stearate

Steric acid

Colloidal silicon dioxide-to confirm the reported incompatibility

Solubilizer

Sodium lauryl sulphate

Drug

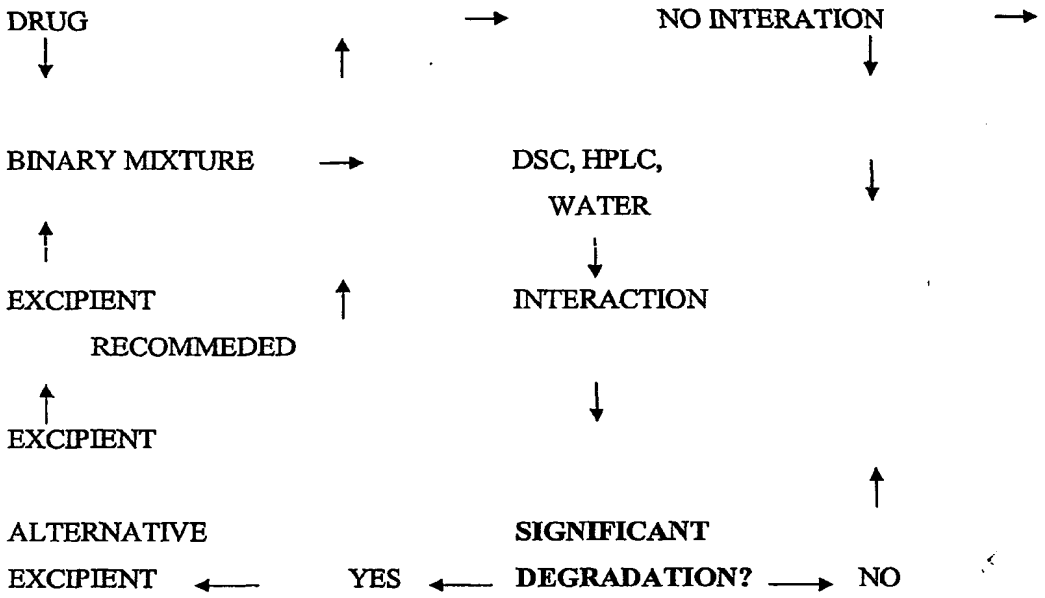
Gabapentin

Binary mixtures to be evaluated (with and without water as necessary):

1. Drug and diluents (1:0.5)
2. Drug and lubricants (1:0.1)
3. Drug and solubilizer (1:0.001)

4. Proposed formulation from the in vitro formulation trials to confirm the extent of interactions and identify suitably stable formulations.
5. Other combinations as appropriate

Scheme to identify chemical compatibility using DSC with confirmatory HPLC.



Significant degradation is defined as

1. >0.5% w/w formation of lactam degradation product at conditions up to 40°C/75%RH.
2. Formation of other degradants at levels >0.1% w/w.
3. Greater relative instability of mixture or formulation to Gabapentin drug substance and Neurotonin capsules.

Storage Conditions

Where humidity controls are not available a defined amount of water may be added to the samples. Storage of samples was in petridishes and in stoppered glass vials.

Analysis of the Samples

The following tests were performed at each interval:

1. Appearance
2. HPLC assay (as for HPLC related substances assay but calibrated for gabapentin resolution rather than for related substances)

The following tests were performed at 14 and 28 day intervals.

1. Appearance
2. HPLC assay
3. HPLC assay for related substances
4. Water (to determine the hygroscopicity of the proposed formulations.

DSC was carried out on initial and end point stability samples.

Acceptance Criteria:

Similar stability profile to Neurotonin capsules, similar stability profile to Gabapentin drug substance, lactam levels <0.5% w/w at 25°C /60%RH and 40°C /75%RH after 28 days, dissolution of the proposed formulation is >80% (Q) in 20 minutes at 25 °C C/60%RH and 40°C /75%RH after 28 days.

Table 25. Pre-formulation studies, Batch Number: GD1

Specification		Initial	25°C/60%RH				40°C/75%RH				50°C				UV (254 nm)
Test	Requirement		3 days	7 days	14 days	28 days	3 days	7 days	14 days	28 days	3 days	7 days	14 days	28 days	3 days
Description	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White pow
Impurities															
a) Lactam content	NMT 0.200%	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—	—	Nil	0.105%	—
b) Single largest individual Impurities	NMT 0.100%	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—	—	Nil	0.020%	—
c) Total other Impurities	NMT 0.500%	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—	—	Nil	0.013%	—
d) Total Impurities	NMT 0.700%	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—	—	Nil	0.138%	—
Assay	95 – 105 %	103.4%	103.3%	103.5%	103.2%	103.2%	103.1%	103.2%	103.1%	102.4%	103.0%	103.1%	102.9%	102.8%	103.5%

— not tested

Table 26. Pre-formulation studies, Batch Number: GD2

Specification		Initial	25°C/60%RH				40°C/75%RH				50°C				UV
Test	Requirement		3 days	7 days	14 days	28 days	3 days	7 days	14 days	28 days	3 days	7 days	14 days	28 days	3 days
Description	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powde
Impurities															
a) Lactam content	NMT 0.200%	Nil	—	—	Nil	0.198%	—	—	0.084%	0.150%	—	—	0.500%	0.540%	—
b) Single largest individual Impurities	NMT 0.100%	0.020%	—	—	0.025%	0.036%	—	—	Nil	Nil	—	—	0.034%	0.042%	—
c) Total other Impurities	NMT 0.500%	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—	—	0.020%	0.028%	—
d) Total Impurities	NMT 0.700%	0.020%	—	—	0.025%	0.234%	—	—	0.084%	0.150%	—	—	0.554%	0.610%	—
Assay	95 – 105 %	101.6%	100.8%	101.0%	101.8%	100.5%	100.4%	100.9%	100.0%	99.9%	100.0%	100.2%	99.8%	99.7%	101.7%

— not tested

Table 27. Pre-formulation studies, Batch Number: GD3

Specification		Initial	25°C/60%RH				40°C/75%RH				50°C				UV
Test	Requirement		3 days	7 days	14 days	28 days	3 days	7 days	14 days	28 days	3 days	7 days	14 days	28 days	3 days
Description	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder
Impurities															
a) Lactam content	NMT 0.200%	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—
b) Single largest individual Impurities	NMT 0.100%	Nil	—	—	Nil	0.008%	—	—	Nil	Nil	—	—	Nil	Nil	—
c) Total other Impurities	NMT 0.500%	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—
d) Total Impurities	NMT 0.700%	Nil	—	—	Nil	0.008%	—	—	Nil	Nil	—	—	Nil	Nil	—
Assay	95 – 105 %	104.4%	104.6%	104.0%	104.7%	104.6%	104.0%	103.8%	103.1%	103.5%	103.8%	103.6%	102.1%	102.5%	104.5%

— not tested

Table 28. Pre-formulation studies, Batch Number: GD4

Specification		Initial	25°C/60%RH				40°C/75%RH				50°C				UV
Test	Requirement		3 days	7 days	14 days	28 days	3 days	7 days	14 days	28 days	3 days	7 days	14 days	28 days	3 days
Description	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder
Impurities															
a) Lactam content	NMT 0.200%	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—
b) Single largest individual Impurities	NMT 0.100%	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—
c) Total other Impurities	NMT 0.500%	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—
d) Total Impurities	NMT 0.700%	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—
Assay	95 – 105 %	99.8%	100.0%	99.9%	101.6%	100.1%	99.8%	99.8%	99.5%	99.6%	99.6%	99.5%	97.8%	98.1%	100.0%

— not tested

Table 29. Pre-formulation studies, Batch Number: GD5

Specification		Initial	25°C/60%RH				40°C/75%RH				50°C				UV
Test	Requirement		3 days	7 days	14 days	28 days	3 days	7 days	14 days	28 days	3 days	7 days	14 days	28 days	2days
Description	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder
Impurities															
a) Lactam content	NMT 0.200%	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—	—	Nil	0.034%	—
b) Single largest individual impurities	NMT 0.100%	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—	—	Nil	0.008%	—
c) Total other impurities	NMT 0.500%	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—
d) Total impurities	NMT 0.700%	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—	—	Nil	0.042%	—
Assay	95 – 105 %	99.1%	99.3%	99.2%	100.6%	100.3%	99.1%	98.9%	99.4%	99.96%	99.6%	99.0%	97.9%	98.7%	99.3%

— not tested

Table 30. Pre-formulation studies, Batch Number: GD6

Specification		Initial	25°C/60%RH				40°C/75%RH				50°C			
Test	Requirement		3 days	7 days	14 days	28 days	3 days	7 days	14 days	28 days	3 days	7 days	14 days	28 days
Description	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder
Impurities														
a) Lactam content	NMT 0.200%	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—	—	Nil	Nil
b) Single largest individual Impurities	NMT 0.100%	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—	—	Nil	Nil
c) Total other Impurities	NMT 0.500%	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—	—	Nil	Nil
d) Total Impurities	NMT 0.700%	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—	—	Nil	Nil
Assay	95 – 105 %	98.4%	—	98.2%	—	98.0%	—	98.1%	—	97.9%	—	98.2%	—	98.1%

— not tested

Table 31. Pre-formulation studies, Batch Number: GD7

Specification		Initial	25°C/60%RH				40°C/75%RH				50°C			
Test	Requirement		3 days	7 days	14 days	28 days	3 days	7 days	14 days	28 days	3 days	7 days	14 days	28 days
Description	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder
Impurities														
a) Lactam content	NMT 0.200%	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—	—	Nil	Nil
b) Single largest individual impurities	NMT 0.100%	Nil	—	—	Nil	Nil	—	—	0.052%	0.049%	—	—	Nil	Nil
c) Total other impurities	NMT 0.500%	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—	—	Nil	Nil
d) Total impurities	NMT 0.700%	Nil	—	—	Nil	Nil	—	—	0.052%	0.049%	—	—	Nil	Nil
Assay	95 – 105 %	98.9%	—	98.7%	—	98.3%	—	98.6%	—	98.2	—	97.7%	—	98.3%

— not tested

Table 32. Pre-formulation studies, Batch Number: GL1

Specification		Initial	25°C/60%RH				40°C/75%RH				50°C				UV
Test	Requirement		3 days	7 days	14 days	28 days	3 days	7 days	14 days	28 days	3 days	7 days	14 days	28 days	3 days
Description	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder
Impurities															
a) Lactam content	NMT 0.200%	Nil	—	—	Nil	0.010%	—	—	Nil	0.050%	—	—	Nil	Nil	—
b) Single largest Individual Impurities	NMT 0.100%	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—	—	Nil	0.009%	—
c) Total other Impurities	NMT 0.500%	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—
d) Total Impurities	NMT 0.700%	Nil	—	—	Nil	0.010%	—	—	Nil	0.050%	—	—	Nil	0.009%	—
Assay	95 – 105 %	100.0%	100.0%	100.1%	100.6%	100.3%	98.6%	98.4%	98.9%	99.3%	99.9%	98.9%	98.8%	98.7%	100.6%

— not tested

Table 33. Pre-formulation studies, Batch Number: GL2

Specification		Initial	25°C/60%RH				40°C/75%RH				60°C				UV
Test	Requirement		3 days	7 days	14 days	28 days	3 days	7 days	14 days	28 days	3 days	7 days	14 days	28 days	3 days
Description	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder
Impurities															—
a) Lactam content	NMT 0.200%	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—
b) Single largest Individual Impurities	NMT 0.100%	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—
c) Total other Impurities	NMT 0.500%	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—
d) Total Impurities	NMT 0.700%	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—
Assay	95 – 105 %	97.5%	97.5%	100.6%	97.6%	–	95.8%	101.2%	96.74%	–	90.3%	86.9%	96.6%	–	100.8%

— not tested

Table 34. Pre-formulation studies, Batch Number: GL3

Specification		Initial	25°C/60%RH				40°C/75%RH				50°C				UV
Test	Requirement		3 days	7 days	14 days	28 days	3 days	7 days	14 days	28 days	3 days	7 days	14 days	28 days	8 days
Description	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder
Impurities															
a) Lactam content	NMT 0.200%	0.095%	—	—	0.100%	0.140%	—	—	0.240%	0.29%	—	—	1.260%	1.050%	—
b) Single largest individual Impurities	NMT 0.100%	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—
c) Total other Impurities	NMT 0.500%	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—
d) Total Impurities	NMT 0.700%	0.095%	—	—	0.100%	0.140%	—	—	0.240%	0.240%	—	—	1.260%	1.050%	—
Assay	95 – 105 %	98.9%	98.9%	97.4%	96.3%	96.31%	99.0%	97.2%	96.2%	96.1%	99.0%	97.3%	95.8%	95.9%	99.2%

— not tested

Table 35. Pre-formulation studies, Batch Number: GS1

Specification		Initial	25°C/60%RH				40°C/75%RH				50°C				UV
Test	Requirement		3 days	7 days	14 days	28 days	3 days	7 days	14 days	28 days	3 days	7 days	14 days	28 days	3 days
Description	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powde
Impurities															
a) Lactam content	NMT 0.200%	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—
b) Single largest individual Impurities	NMT 0.100%	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—
c) Total other Impurities	NMT 0.500%	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—
d) Total Impurities	NMT 0.700%	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—
Assay	95 – 105 %	105.2%	104.3%	101.9%	104.2%	101.2%	97.5%	101.5%	97.1%	100.9%	99.4%	104.6%	103.5%	100.9%	105.6%

— not tested

Table 36. Pre-formulation studies, Blend I

Specification		Initial	25°C/60%RH				40°C/75%RH				50°C			
Test	**Requirement**		**3 days**	**7 days**	**14 days**	**28 days**	**3 days**	**7 days**	**14 days**	**28 days**	**3 days**	**7 days**	**14 days**	**28 days**
Description	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder
Impurities														
a) Lactam content	NMT 0.200%	Nil	—	—	Nil	Nil	—	—	Nil	0.062%	—	—	0.097%	0.130%
b) Single largest individual impurities	NMT 0.100%	Nil	—	—	Nil	Nil	—	—	Nil	0.007%	—	—	Nil	Nil
c) Total other impurities	NMT 0.500%	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—	—	Nil	Nil
d) Total impurities	NMT 0.700%	Nil	—	—	Nil	Nil	—	—	Nil	0.069%	—	—	0.097%	0.130%
Assay	95 – 105 %	102.5%	—	102.0%	101.9%	101.95	—	101.8%	101.4%	101.1%	—	101.9%	101.2%	101.9%

— not tested

Table 37. Pre-formulation studies, Blend II

Specification		Initial	25°C/60%RH				40°C/75%RH				50°C			
Test	Requirement		3 days	7 days	14 days	28 days	3 days	7 days	14 days	28 days	3 days	7 days	14 days	28 days
Description	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder
Impurities														
a) Lactam content	NMT 0.200%	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—	—	Nil	0.030%
b) Single largest individual impurities	NMT 0.100%	Nil	—	—	Nil	0.007%	—	—	Nil	Nil	—	—	Nil	Nil
c) Total other impurities	NMT 0.500%	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—	—	Nil	Nil
d) Total impurities	NMT 0.700%	Nil	—	—	Nil	0.007%	—	—	Nil	Nil	—	—	Nil	0.030%
Assay	95 – 105 %	102.8%	—	102.5%	102.4%	101.1%	—	102.2%	101.8%	101.1%	—	102.0%	101.7%	102.6%

— not tested

Table 38. Pre-formulation studies, Neurontin® Capsules 400mg, Batch Number: 0015077

Specification		Initial	25°C/60%RH				40°C/75%RH				50°C			
Test	Requirement		3 days	7 days	14 days	28 days	3 days	7 days	14 days	28 days	3 days	7 days	14 days	28 days
Description	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder
Impurities														
a) Lactam content	NMT 0.200%	Nil	—	—	0.040%	Nil	—	—	0.046%	Nil	—	—	0.058%	Nil
b) Single largest individual Impurities	NMT 0.100%	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—	—	Nil	Nil
c) Total other Impurities	NMT 0.500%	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—	—	Nil	Nil
d) Total Impurities	NMT 0.700%	Nil	—	—	0.040%	Nil	—	—	0.046%	Nil	—	—	0.058%	Nil
Assay	95 – 105 %	102.7%	—	102.4%	102.5%	—	—	102.1%	101.8%	—	—	101.9%	101.9%	—

— not tested

Table 39. Pre-formulation studies, Drug Substance, Gabapentin Lot number: R 90562

Specification		Initial	25°C/60%RH				40°C/75%RH				50°C			
Test	Requirement		3 days	7 days	14 days	28 days	3 days	7 days	14 days	28 days	3 days	7 days	14 days	28 days
Description	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder
Impurities														
a) Lactam content	NMT 0.200%	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—	—	0.004%	0.004%
b) Single largest individual impurities	NMT 0.100%	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—	—	Nil	Nil
c) Total other impurities	NMT 0.500%	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—	—	Nil	Nil
d) Total impurities	NMT 0.700%	Nil	—	—	Nil	Nil	—	—	Nil	Nil	—	—	Nil	Nil
Asay	95 – 105 %	99.4%	—	98.6%	98.6%	98.51%	—	98.53%	98.4%	97.79%	—	98.5%	98.5%	98.1%

— not tested

Preformulation conclusions

The excipient compatibility study reveals that commonly used pharmaceutical excipients are compatible with gabapentin. The excipients studied do not adversely affect the stability of gabapentin when stored at 25°C/60%RH and 40°C/75%RH.

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. It is intended, therefore, that the invention be defined by the scope of the claims that follow and that such claims be interpreted as broadly as is reasonable.